Phase I and Clinical Pharmacological Evaluation of Pirozantrone Hydrochloride (Oxantrazole)

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ABSTRACT

Pirozantrone hydrochloride, an anthrapyrazole analogue, was selected for clinical evaluation based on broad antitumor activity against murine tumor systems and on potentially less cardiotoxicity when compared to anthracyclines. This anthrapyrazole analogue is currently under clinical evaluation, and we now report results on a Phase I clinical trial incorporating a pharmacologically guided dose-escalation scheme. Dose escalation was designed to proceed by factors of 2 until the patient drug exposure (concentration × time) was 40% of the murine exposure at the LD10 dose (90 mg/m²). Thereafter, more moderate dose escalations were employed. The target concentration × time value (59 µg-min/ml) derived from preclinical pharmacology data was exceeded in all three patients at a dose of 90 mg/m². A dose of 160 mg/m² was found to reproducibly result in appropriate myelosuppression. This dose is recommended for further testing in Phase II studies. Nonhematological toxicities encountered in this trial were mild, the most notable being phlebitis at the infusion site. Objective responses were observed in two patients, one with metastatic breast cancer and another with metastatic melanoma. Following a 60-min infusion, pirozantrone hydrochloride plasma elimination was monoeponential, with a half-life of approximately 30 min, mean total body clearance of 1.29 liters/min/m², and mean steady state volume of distribution of 29 liters/m².

INTRODUCTION

The important role of anthracycline antibiotics in cancer chemotherapy has prompted many efforts to develop analogues which retain broad spectrum clinical activity but have reduced toxicity. One effort has focused on anthrapyrazoles, compounds derived by modification of the anthracenedione nucleus in order to reduce the formation of semiquinone free radicals, which are possibly responsible for anthracycine-induced cardiotoxicity (1). Among anthrapyrazole derivatives, pirozantrone hydrochloride (NSC 349174, oxantrazole) was selected for clinical study based on broad activity against murine tumor model systems (2, 3). In addition, superoxide dismutase-sensitive oxygen consumption (a measure of free radical formation) in rat liver microsomal preparations (4) and toxicity in fetal mouse organ culture assay were both reduced for pirozantrone hydrochloride, when compared to doxorubicin (5). As with other anthracycline-like analogues, pirozantrone hydrochloride has been shown to intercalate into DNA, to inhibit DNA synthesis, and to introduce DNA strand breaks in murine and human tumor cells exposed to the drug in culture (4, 6).

Following i.p. administration of pirozantrone hydrochloride to mice, survival was increased in animals implanted with B-16 melanoma, M5076 sarcoma, L1210 and P-388 leukemias, and MX-1 mammary xenograft (2, 3). Data are contradictory with regard to pirozantrone hydrochloride activity against anthracycline-resistant cell lines (2, 3). No marked schedule dependency was observed in mice with i.p. implanted L1210 leukemia. The single-dose combined-sex LD10 value for pirozantrone was 75 mg/m² (7). Myelosuppression and testicular atrophy were the major toxicities in beagle dogs (7).

Review of many NCI-sponsored Phase I clinical trials showed that most required more patients than anticipated to reach the maximally tolerated dose (8). In many instances this was due to differences in drug elimination between mice and humans, resulting in less drug exposure in humans compared to mice for an equivalent body surface area (m²) dose. One approach to this problem is to develop schemes which compare drug exposure rather than dose when attempting to define a maximally tolerated dose in humans based on LD10 data from mice. Collins et al. (8) proposed two pharmacologically guided dose-escalation schemes for Phase I trials based on preclinical mouse plasma C × T data and human plasma C × T data obtained subsequently during Phase I trials. One of these pharmacologically guided dose escalation schemes was selected for use in this pirozantrone hydrochloride clinical trial, making this Phase I clinical trial the first prospective study of pharmacologically guided dose-escalation in the United States. We previously reported preclinical pharmacology of pirozantrone hydrochloride in mice, including the relevant C × T data to be applied to the Phase I dose-escalation scheme (6). We now report results of our Phase I clinical trial and pharmacokinetic study with this agent, including data on the pharmacologically guided dose-escalation scheme.

MATERIALS AND METHODS

Thirty-two patients were entered on this clinical protocol, 2 of whom were not treated due to a rapid deterioration in their clinical condition. Characteristics of the 30 treated patients are outlined in Table 1. Patients considered for study had histological or cytological confirmation of unsectetable cancer (excluding leukemia) for which there was no conventional therapy that offered a more reasonable hope of cure or significant palliation. All patients were ambulatory and in a reasonable state of nutrition. Patients were required to have a WBC count ≥ 4,000/mm³, platelet count ≥ 130,000/mm³, hemoglobin ≥ 10 g/dl, alkaline phosphatase and serum serum glutamate-oxalacetate transaminase ≤ 3 times normal, serum creatinine < 0.3 mg/dl above the upper limit of institutional normal value, and an Eastern Cooperative Oncology Group performance status of 0, 1, or 2. Patients were excluded if they had uncontrolled infections, New York Heart Association classification III or IV, significant arrhythmia such as atrial fibrillation or uncontrolled frequent ventricular ectopy, myocardial infarction within 6 months, or a history of congestive heart failure. Patients were also excluded if they had a known central nervous system metastasis or seizure disorder, major surgery within the preceding 21 days, previous radiation to >30% of their bone marrow, concurrent radiotherapy, and to introduce DNA strand breaks in murine and human tumor cells exposed to the drug in culture (4, 6).

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patients with stable or responding disease were considered for retreatment every 3 weeks. Those without significant toxicity at a given dose level were retreated with a dose escalation, while those with acceptable toxicity were retreated at the same dose level. Dose reductions were allowed for subsequent treatment courses as clinically indicated.

Chemicals. Pirozantrone hydrochloride for laboratory use was provided by the Pharmaceutical Resources Branch, Division of Cancer Treatment, National Cancer Institute (Bethesda, MD), the internal standard (PD1188616) was generously provided by Warner-Lambert Parke-Davis. Disposable extraction columns (C18, 1 ml) were purchased from J. T. Baker (Phillipsburg, NJ). Hilar HPLC columns were purchased from Merck (Darmstadt, FRG). All other solvents and reagents were of HPLC or chromatographic grade.

HPLC Assay for Pirozantrone Hydrochloride. The method for determination of pirozantrone hydrochloride in plasma and urine has been described (9). Briefly, immediately after obtaining blood in evacuated citrated tubes, 200 μl of 1.2 M citric acid/25% sodium acetate (pH 4.0) were added to each tube to prevent oxidation of pirozantrone hydrochloride. Twenty-five ml of the same citric acid/ascorbate solution were added to urine containers for collection of 48-h urine specimens. Plasma and urine (0.1–1.0 ml) were diluted to a final volume of 1.0–1.5 ml with 0.05 M sodium phosphate buffer (pH 6.0). Internal standard (100–500 ng dissolved in 0.02 M sodium acetate, pH 4.0) was added to each plasma and urine sample. Samples were then applied to C18 disposable 1-ml extraction columns prepared by washing with methanol, water, and 0.05 M sodium phosphate buffer, pH 6.0 (2 ml each). Following sample application, columns were washed with 0.05 M sodium phosphate buffer, pH 6.0 (2 ml). Pirozantrone hydrochloride and internal standard were then eluted with 1 ml of a mixture of methanol, glacial acetic acid, and 0.02 M sodium acetate buffer, pH 4.0 (12:13:1, v/v/v). Eluates were evaporated to dryness under nitrogen and the residue was dissolved in 100–200 μl of mobile and then to HPLC analysis. Drug and internal standard were analyzed by reverse phase HPLC on a Hilar RP-2 column with a mobile solvent system of dimethylformamide-acetonitrile/0.2 M ammonium acetate, pH 4.5 (20:5:75), at a flow rate of 1 ml/min. A 5-cm guard column packed with C8 pellicular resin was used for plasma and urine analyses. Detection of pirozantrone hydrochloride and the internal standard was by visible light absorption at 514 nm.

Pharmacokinetic Analysis. Area under the plasma concentration versus time curves (C × T), CLtrb, and Vcritical were calculated using the trapezoidal rule and noncompartmental methods. Vcritical was corrected for the length of infusion. Renal clearance was calculated as the product of the fraction of dose recovered in urine and CLtrb.

RESULTS

Toxicity. Significant hematological toxicity was not observed at doses <140 mg/m². The lowest nadir WBC at these doses was 2600/mm³. The lowest nadir WBC counts from the six patients initially treated with 140 mg/m² ranged from 1600/mm³ to 3800/mm³ (mean, 2600/mm³). One patient had a platelet nadir of 56,000/mm³ following a drug dose of 140 mg/m². This patient had received whole brain radiation therapy for a brain metastasis which became clinically evident shortly after initiation of pirozantrone hydrochloride treatment. No other patient in this study had a platelet count <87,000/mm³. The WBC nadirs for the six patients treated at 160 mg/m² ranged from 1500 to 2200/mm³ (mean, 1800/mm³). The first cycle WBC nadir for the 12 patients treated at doses of 140 or 160 mg/m² occurred between 7 and 22 days after treatment, with 10 of these nadirs occurring between 13 and 19 days. WBC counts recovered to ≥3500/mm³ in all 12 patients by 33 days after treatment. We did not escalate doses higher than 160 mg/m², because this dose reproducibly produced leukopenia to an appropriate degree and, additionally, unacceptable severe myelosuppression was observed in two patients treated at 190 mg/m².

Table 1 Patient profile

<table>
<thead>
<tr>
<th>Total number of treated patients</th>
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<td>Male/female</td>
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<tr>
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<td>11</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Median age (range)</td>
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* Eastern Cooperative Oncology Group.

Table 2 Individual doses

<table>
<thead>
<tr>
<th>Dose (mg/m²)</th>
<th>No. of new patients</th>
<th>No. of patients treated</th>
<th>No. of cycles</th>
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</tr>
<tr>
<td>160</td>
<td>6</td>
<td>6</td>
<td>16</td>
</tr>
</tbody>
</table>

Table 2 Individual doses

frequent vomiting, severe anorexia, or any chemotherapy within the proceeding 3 weeks (5 weeks for mitomycin C or nitrosoureas). Study patients could not have received prior anthracycline or mitoxantrone therapy.

Tests done prior to entry into study included a history, physical examination, tumor measurement whenever possible, WBC count, hemoglobin determination, platelet count, chemistry group, chest X-ray, electrocardiogram, urinalysis, iothalamate renal clearance, and electroencephalogram.

Patients were entered in groups of three at each dose level. New patients were entered at a higher dose level only after the three patients treated at the previous level had been observed for a minimum of 3 weeks after treatment. Dose levels for new patients were determined based on the available pharmacokinetic (C × T) data from patients treated at the previous dose level. If the mean C × T value for the previous three patients was less than 59 μg-min/ml (40% of the mouse C × T at the mouse LD10 dose; see “Results”), then the pirozantrone dose was doubled for the subsequent three dose levels. If the mean C × T value was ≥59 μg-min/ml, then subsequent dose escalations were not to exceed 133% of the previous dose level. New patients were entered at pirozantrone hydrochloride doses of 7.5, 15, 30, 45, 90, 120, 140, and 160 mg/m². The total cumulative pirozantrone dose was <300 mg/m² in 24 patients. The remaining patients received total doses of 320, 480, 510, 980, 1030, and 1280 mg/m². The number of new patients and the total number of patients treated at each dose level are shown in Table 2.

Initially, pirozantrone hydrochloride was diluted in 50 ml D5W and administered as a 1-h i.v. infusion. After some patients experienced local venous irritation, the drug was diluted in 300 ml D5W. Individual
m² during a concurrent Phase I study at The Johns Hopkins Hospital.

Nonhematological toxicities included mild to moderate alopecia in 12 of 30 patients. Grade 1–2 anorexia, nausea, and vomiting were observed in 17 patients but did not appear to be dose related. Mild to moderate stomatitis and diarrhea were reported in 3 and 4 patients, respectively. Phlebitis at the infusion site was a bothersome problem in 7 patients. In light of this, the pirozantone was infused in a more dilute solution (300 versus 50 ml) to patients receiving higher drug doses. No hepatic, renal, or neurological toxicity was attributed to the drug.

In view of the well established association between anthracyclines and cardiac toxicity, cardiac parameters were closely monitored in the study patients. Initially, the 1-h drug administration was accompanied by continuous electrocardiographic monitoring. No significant cardiac dysrhythmias were noted in 10 patients treated in this manner. It was then reported by the NCI that one patient treated at another institution had frequent premature ventricular contractions following pirozantone hydrochloride. Subsequently, patients were asked to wear a Holter monitor overnight prior to drug treatment and for 24 h following pirozantone administration. After the first course of treatment, these patients were monitored for 2 h prior to and 15 h after treatment. There were no significant cardiac arrhythmias noted in these patients. However, one patient, a 62-year-old female, had several brief episodes of Mobitz I second degree atrioventricular heart block over a span of 2 min (within 10 min following completion of 140 mg/m² pirozantone hydrochloride). This patient did not have Holter monitor abnormalities with her preceding course of pirozantone hydrochloride. Based on the lack of significant cardiac dysrhythmias attributable to pirozantone in the 17 patients who were Holter monitored, we did not require cardiac monitoring for the last 3 patients entered in this study.

There was no clinical evidence of cardiac muscle compromise in the treated patients (no cardiomegaly or congestive heart failure). Cardiac ejection fractions were obtained for 3 patients following total cumulative pirozantone doses of 480, 840, and 1030 mg/m². None of these studies demonstrated evidence of cardiac muscle dysfunction.

Responses. Two of the 30 patients had objective evidence of antitumor activity with pirozantone hydrochloride. One was a 52-year-old female with metastatic breast cancer who had developed bone disease progression following previous therapy with multiple sequential hormones and combination chemotherapy (cyclophosphamide, 5-fluorouracil, prednisone, and then 5-fluorouracil plus leucovorin). This patient received 140 mg/m² doses of pirozantone and subsequently had marked subjective and objective (recalification of a measurable lytic bone lesion) evidence of tumor regression. She received 7 cycles of therapy, with a time to treatment failure of 6 months.

The other responding patient was a 55-year-old female with metastatic breast cancer who had developed bone disease progression following previous therapy (cyclophosphamide, 5-fluorouracil, prednisone, and then 5-fluorouracil plus leucovorin). This patient received 140 mg/m² doses of pirozantone and subsequently had marked subjective evidence of tumor regression. She received 7 cycles of therapy, with a time to treatment failure of 6 months.

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Further dose escalations were based on a modified Fibonacci scheme.

Pharmacokinetic parameters could be reliably calculated for the 15 patients who received doses of 45–160 mg/m². Peak plasma concentrations at the end of the 60-min i.v. infusion increased with dose and were 1.6–2.2 µg/ml for the 3 patients who received 160 mg/m² dose (Fig. 1). After the end of infusion, plasma levels declined in a monoexponential fashion, with a $t_\text{1/2}$ of approximately 30 min. There may have been terminal phases of elimination, but it was not possible to accurately describe plasma elimination of pirozantrone hydrochloride with multicompartment models.

For these 15 patients, the mean $C_{\text{LB}}$ was 1.29 liters/min/m² and the mean $V_{\text{a}}$ was 29 liters/m² or 0.8 liters/kg (Table 4). The intersubject variation was 25% for $CL_{\text{LB}}$ and 38% for $V_{\text{a}}$. The 60-min infusion time was large compared with the 30-min half-life, which tends to increase the uncertainty in $V_{\text{a}}$. The mean recovery of pirozantrone hydrochloride in 48-h urine was 5.3% of the i.v. dose and the mean renal clearance was 68.4 ml/min/m².

Fig. 2 shows the plasma concentration versus time profiles for mice at 90 mg/m² (120% of LD$_{10}$) and humans at 160 mg/m² (maximally tolerated dose). Although the mice received a bolus injection while humans received a 60-min infusion, the overall patterns of qualitative drug exposure are quite similar. Quantitatively, the ratio of $C \times T$ values was 0.86 when the murine values are linearly adjusted to 75 mg/m², the LD$_{10}$. In contrast, the dose ratio (maximally tolerated dose/LD$_{10}$) was 2.1 (160/75).

**Fig. 1.** Peak plasma concentrations of pirozantrone hydrochloride at the completion of the 60-min infusion plotted as a function of dose.

**Fig. 2.** Comparison of plasma concentration versus time profiles. Mice (•) received 90 mg/m² (120% of LD$_{10}$). Human (■) received 160 mg/m² (maximally tolerated dose).

**DISCUSSION**

In this Phase I trial, there was less nonhematological toxicity associated with pirozantrone hydrochloride than would be expected with doxorubicin doses that cause similar degrees of hematological toxicity. Pirozantrone hydrochloride doses of ≥140 mg/m² were generally well tolerated, with most patients reported mild (or less) nausea, vomiting, alopecia, or stomatitis. The one observed toxicity which was more common with pirozantrone hydrochloride was phlebitis at the infusion site. This toxicity was also observed with menogaril (10) and bisantrene (11, 12). There were no instances of drug extravasation and thus no comment can be made on the vesicant properties of this drug in humans. Cardiac toxicity was not observed in this Phase I trial, despite total cumulative drug doses which ranged up to 1280 mg/m². This is consistent with preclinical information suggesting that pirozantrone hydrochloride may have less cardiac toxicity than doxorubicin. Additional data would be required to confirm this hypothesis.

Based on the data from our trial, an initial dose of 160 mg/m² is recommended for Phase II testing. The disease responses we observed in a patient with metastatic breast cancer and another patient with advanced melanoma support the further testing of this agent in these diseases.

This Phase I clinical trial incorporated a pharmacologically guided dose-escalation scheme in place of traditional Fibonacci-based dose escalations. As discussed by Collins et al. (8), such an escalation scheme, based on drug exposure rather than drug dose, is of particular benefit if the drug is eliminated more efficiently by humans than by mice. In that circumstance, one would predict that traditional dose-escalation schemes, which are based solely on toxicity rather than on exposure, would require greater numbers of escalations to define the maximally tolerated dose. This in turn would require greater numbers of patients for such trials (8).

In preclinical pharmacology studies with pirozantrone hydrochloride, we determined that the parent drug was much less stable in fresh human plasma ($t_\text{1/2} < 5$ min) than in fresh mouse plasma ($t_\text{1/2} = 105$ min) (6). This rapid degradation in fresh human plasma might lead to more rapid elimination in humans than in mice. Drug elimination was more rapid in humans than in mice, and total body clearance was almost 3 times greater in humans (1290 versus 458 ml/min/m²). The assay for parent drug was not as sensitive as those for some anthracyclines with prolonged elimination phases, and we may have failed to detect terminal phases of elimination of pirozantrone hydrochloride in humans. However, since the same assay was employed in all our studies, the species comparisons seem warranted.

The marked differences in plasma pharmacokinetics of pirozantrone hydrochloride in mice and humans were reflected in drug exposure ($C \times T$) values for the two species. The $C \times T$ values for a pirozantrone hydrochloride dose of 90 mg/m² for mice and for humans were 177 µg-min/ml (6) and 87 µg-min/ml, respectively. Consistent with those data are the very similar plasma concentration-time profiles for mice receiving doses of 90 mg/m² and patients receiving doses of 160 mg/m² (Fig. 2). Recall that 90 mg/m² was 120% of the LD$_{10}$ dose in mice, while 160 mg/m² was the maximally tolerated dose in this Phase I study. These data show that the more rapid metabolism of pirozantrone hydrochloride in humans, at least partially due to rapid degradation in human plasma, leads to reduced drug exposure when compared to equivalent doses in mice. Applying the pharmacologically guided dose-escalation scheme in this situation, we were able to reach the maximally
tolerated dose in this trial with 6–9 fewer patients than would have been required with a modified Fibonacci escalation scheme.

The pharmacokinetics of pirozantrone hydrochloride in mice (relatively prolonged plasma elimination, large volume of distribution, rapid clearance, and low urinary recovery of parent drug) were similar to those of anthracyclines and other related molecules in animals and humans (13–16). In humans, pirozantrone hydrochloride pharmacokinetics appeared to be quite different from those of anthracycline-like agents. Doxorubicin and similar molecules frequently have terminal elimination-phase half-life values of approximately 30 h and total body clearance values of 500 mg/min/2 in humans (14, 16). In contrast, pirozantrone hydrochloride elimination-phase half-life values were less than 1 h. However, as already noted, the pirozantrone hydrochloride assay was less sensitive than those for doxorubicin and other anthracyclines, and there may well have been terminal elimination phases not detected with our method. Differences in plasma elimination between pirozantrone hydrochloride and anthracyclines may be less pronounced than apparent from our data. Pirozantrone hydrochloride pharmacokinetics are of even more interest in light of the fact that the two major metabolic pathways for doxorubicin, reduction to an alcohol and formation of aglycones, are not available for pirozantrone hydrochloride. We conclude that the very rapid plasma elimination is at least partially a consequence of the rapid pirozantrone hydrochloride degradation in human plasma.

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Phase I and Clinical Pharmacological Evaluation of Pirozantrone Hydrochloride (Oxantrazole)


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